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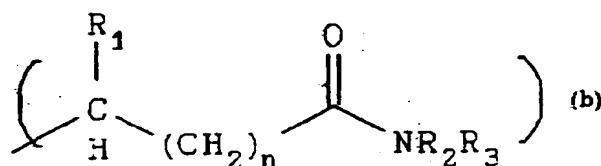
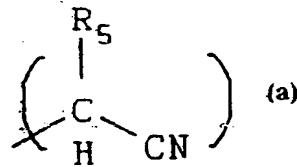
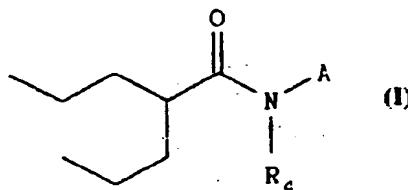
PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :		A1	(11) International Publication Number:	WO 95/01956
C07C 237/12, 237/22, 233/01, A61K 31/16, 31/275			(43) International Publication Date:	19 January 1995 (19.01.95)
(21) International Application Number:	PCT/US94/07498			
(22) International Filing Date:	6 July 1994 (06.07.94)			
(30) Priority Data:	08/088,074 6 July 1993 (06.07.93)	US		
(60) Parent Application or Grant			(81) Designated States:	AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(63) Related by Continuation				
US Filed on	08/088,074 (CIP) 6 July 1993 (06.07.93)			
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(54) Title: DERIVATIVES OF VALPROIC AND 2-VALPROENOIC ACID AMIDES AND USE AS ANTICONVULSANTS



(57) Abstract

A compound having structure (I), wherein A is X or Y, X is (a), Y is (b); R₁, R₂, R₃, R₄ and R₅ are each independently hydrogen, a C₁-C₆ alkyl group, an aralkyl group, or an aryl group; and n is 0, 1, 2, or 3. Also provided are a compound containing a 2-valproenoic moiety, pharmaceutical compositions comprising these compounds, and methods of using them for the effective treatment of epilepsy and other neurological disorders.

Applicants: Mitchell Shirvan et al.
 Serial No.: Not Yet Known
 Filed: Herewith
 Exhibit 2

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DERIVATIVES OF VALPROIC AND 2-VALPROENOIC ACID AMIDES AND USE AS ANTICONVULSANTS

Background of the Invention

The invention relates to new derivatives of 2-propylpentanoic acid (valproic acid, hereinafter VPA), and 2-propyl-2-pentenoic acid, their preparation and use as antiepileptic agents.

VPA and its alkali salts are major drugs in the arsenal of drugs for the treatment of epileptic seizures and convulsions. However, approximately 25% of epileptic patients do not respond to current treatment. Furthermore, VPA itself has considerable adverse effects including hepatotoxicity and teratogenicity. Baille, T.A. and A.W. Rettenmeier, in "Antiepileptic Drugs," ed. by R.H. Levy, F.E. Dreifuss, R.H. Mattson, B.S. Meldrum and J.K. Penry, Raven Press, New York (1989), at 601-619.

One approach to obtain improved antiepileptic agents has been to prepare the primary amide derivatives of VPA and its analogs. M. Bialer, Clin. Pharmacokinet. 20: 114-122 (1991); M. Bialer, A. Haj-Yehia, N. Barzaghi, F. Pisani, and E. Perucca, Eur. J. Clin. Pharmacol., 289-291 (1990); A. Haj-Yehia and M. Bialer, J. Pharm. Sci., 79: 719-724 (1990). While certain glycinamide derivatives have been disclosed by R. Roncucci, et al., U.S. Patent 4,639,468, issued January 27, 1987, these compounds generally have not been accepted into clinical practice. Thus, an urgent need still exists in the art for developing anti-convulsant agents with improved efficacy and a wider margin between the dose which is therapeutic and that which is neurotoxic.

VPA and 2-ene-VPA-related glycine amides have been disclosed by Granneman, et al., Xenobiotica, 14, 375 (1984), to be minor metabolites of VPA. However, an examination of the mass spectral data therein shows that

-2-

those compounds are in fact VPA and 2-ene-VPA glycine and cannot be glycinamide conjugates, wherein the glycine nitrogen moiety is attached to the VPA or 2-ene-VPA carbonyl. While Granneman, et al., described these 5 compounds as glycine conjugates, they erroneously named them as VPA and 2-ene-VPA glycinamides, rather than valproyl and 2-ene-VPA glycine; the latter names are in accord with the method of preparation and the mass spectral data reported by Granneman, et al.

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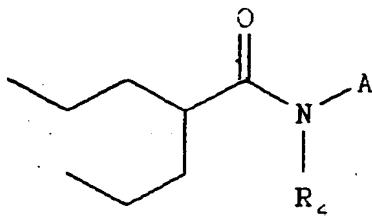
- 3 -

Summary of Invention

This invention provides a compound having general structure I as follows:

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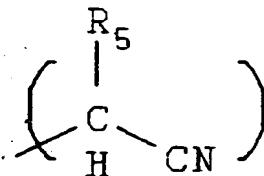
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wherein A is X or Y,

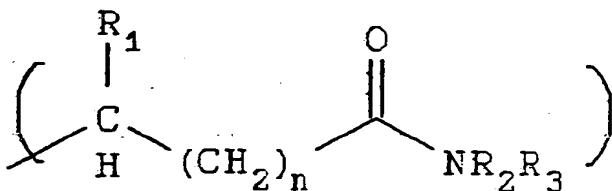
X comprises

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20 Y comprises

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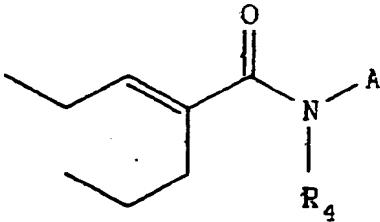


R₁, R₂, R₃, R₄ and R₅ are each independently hydrogen, a C₁-C₆ alkyl group, an aralkyl group, or an aryl group; and n is 0, 1, 2, or 3.

30

This invention provides a compound of general formula II as follows:

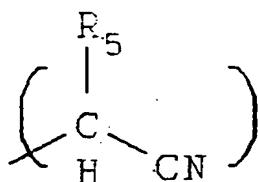
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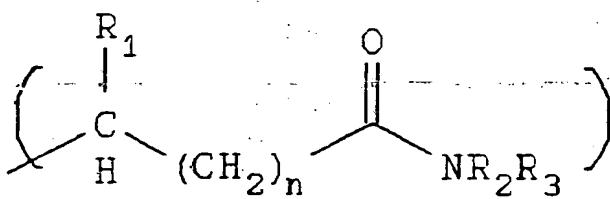
wherein A is X or Y,
 X comprises

5



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R₁, R₂, R₃, R₄ and R₅ are each independently hydrogen, a C₁-C₆ alkyl group, an aralkyl group, or an aryl group; and n is 0, 1, 2, or 3.

20 This invention provides pharmaceutical compositions which comprise a compound of general formula I or II or a pharmaceutically acceptable salt thereof in a therapeutically effective amount and a pharmaceutically acceptable carrier.

25

This invention provides methods of treating a subject afflicted with epilepsy, affective illness, cognitive disorders, neurodegenerative disease, or dyskinesiae, neurotoxic injury, of alleviating convulsions in a 30 subject afflicted with epilepsy, of treating a subject afflicted with stroke, or brain ischemia which comprises administering to the subject an effective amount of the compound of general formula I or II.

-5-

Brief Description of the Drawings:

A more complete understanding of the invention and many of its advantages will become apparent by reference to the detailed description which follows when considered in conjunction with the accompanying figures wherein:

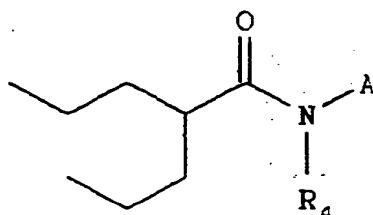
- Figure 1 illustrates performance in the passive avoidance test of rats treated with the indicated drugs for the duration of 28 days at the following daily oral doses:
- 10 Compound 1, 200mg/kg; VPA, 500mg/kg. Tests were performed on day 10 after drug treatment. Latency, in seconds, represents response time to entry into dark compartment. Maximum latency is 300 sec. Longer latencies represent improved performance. Bars represent mean standard error
15 (SEM).

- Figure 2 illustrates performance in the active avoidance test of rats treated with the indicated drugs for the duration of 28 days at the following daily oral doses:
- 20 Compound 1, 200mg/kg, VPA, 500 mg/kg. Test was performed on days 16-17 (session 1) and 22-23 (session 2) after initiation of drug treatment. Better performance is indicated by an increase in avoidance score, a decrease in latency time, and an increase in the number of
25 crossings.

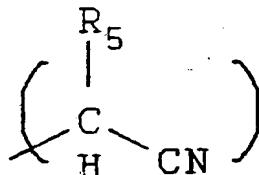
- 6 -

Description of the Invention

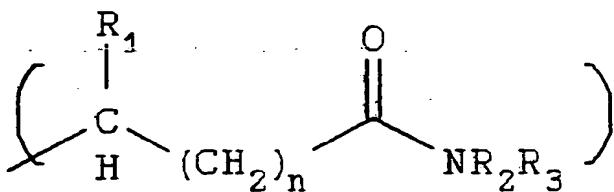
Compounds of particularly high activity and low toxicity result from the coupling of VPA at the carboxyl group with amino acid amides. This invention provides a compound of general formula I as follows:



wherein A is X or Y,
15 X comprises



25



R_1 , R_2 , R_3 , R_4 and R_5 are each independently hydrogen, a C₁-C₆ alkyl group, an aralkyl group, or an aryl group; and n is 0, 1, 2, or 3.

In an embodiment, A is Y; and R₄ is hydrogen.

35 In another embodiment, the invention provides the compound of formula I hereinabove shown wherein the C₁-C₆ alkyl group is a linear chain alkyl group. In another embodiment, the invention provides the compound of

- 7 -

formula I hereinabove shown wherein the C₁-C₆ alkyl group is a branched chain alkyl group. In yet another embodiment, the invention provides the compound of formula I hereinabove shown wherein the aralkyl group is 5 a benzyl, alkylbenzyl, hydroxybenzyl, alkoxycarbonylbenzyl, aryloxycarbonylbenzyl, carboxybenzyl, nitrobenzyl, cyanobenzyl, or halobenzyl group. In still another embodiment, the invention provides the compound of formula I wherein the aryl group 10 is a phenyl, naphthyl, anthracenyl, pyridinyl, indolyl, furanyl, alkylphenyl, hydroxyphenyl, alkoxycarbonylphenyl, aryloxycarbonylphenyl, nitrophenyl, cyanophenyl, halophenyl group, mercaptophenyl, or aminophenyl group.

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In preferred embodiments, examples of the compound according to the invention include:

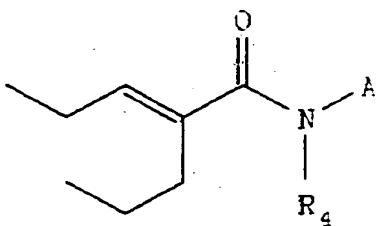
N-(2-n-propylpentanoyl)glycinamide;
N-(2-n-propylpentanoyl)-N-methyl-glycinamide;
20 N-(2-n-propylpentanoyl)glycine-N'-methylamide;
N-(2-n-propylpentanoyl)glycine-N'-butylamide;
N-(2-n-propylpentanoyl)leucinamide;
N-(2-n-propylpentanoyl)alanine-N'-benzylamide;
N-(2-n-propylpentanoyl)alaninamide;
25 N-(2-n-propylpentanoyl)-2-phenylglycinamide;
N-(2-n-propylpentanoyl)-4-aminobutyramide;
N-(2-n-propylpentanoyl)-β-alaninamide;
N-(2-n-propylpentanoyl)threoninamide;
N-(2-n-propylpentanoyl)glycine-N',N'-dimethylamide;
30 and N-(2-n-propylpentanoyl)aminoacetonitrile.

In addition, novel compounds of general formula II exhibiting high activity and low toxicity are related to those of general formula I, except for having a double bond in the 2-position.

This invention therefore provides a compound of general formula II as follows:

- 8 -

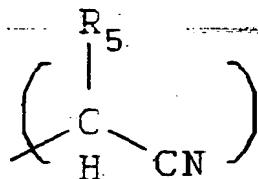
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wherein A is X or Y,

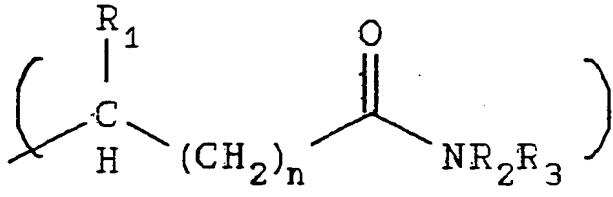
10 X comprises

15



Y comprises

20



R₁, R₂, R₃, R₄ and R₅ are each independently hydrogen, a C₁-C₆ alkyl group, an aralkyl group, or an aryl group; and n is 0, 1, 2, or 3.

In an embodiment, A is Y; and R₄ is hydrogen.

30 In another embodiment, this invention provides the compound of formula II hereinabove shown wherein the C₁-C₆ alkyl group is a linear chain alkyl group. In another embodiment, the invention provides the compound of formula II hereinabove shown wherein the C₁-C₆ alkyl group
35 is a branched chain alkyl group. In still another embodiment, the invention provides the compound of formula II hereinabove shown wherein the aralkyl group is a benzyl, alkylbenzyl, hydroxybenzyl, alkoxy-

-9-

carbonylbenzyl, aryloxycarbonylbenzyl, carboxybenzyl, nitrobenzyl, cyanobenzyl, or halobenzyl group. In yet another embodiment, the invention provides the compound of formula II hereinabove shown wherein the aryl group is 5 a phenyl, naphthyl, anthracenyl, pyridinyl, indolyl, furanyl, alkylphenyl, hydroxyphenyl, alkoxy carbonylphenyl, aryloxycarbonylphenyl, nitrophenyl, cyanophenyl, halophenyl group, mercaptophenyl, or aminophenyl group.

10

In preferred embodiments, examples of the compound according to the invention include:

- N-(2-n-propylpent-2-enoyl)glycinamide;
N-(2-n-propylpent-2-enoyl)alaninamide; and
15 N-(2-n-propylpent-2-enoyl)glycine-N'-methylamide.

The invention further provides a pharmaceutical composition which comprises any compound hereinabove shown or a pharmaceutically acceptable salt thereof in a 20 therapeutically effective amount and a pharmaceutically acceptable carrier. The invention provides a pharmaceutical composition wherein the therapeutically effective amount is an amount from about 10 to about 500 mg. The invention encompasses a pharmaceutical 25 composition as hereinabove described wherein the carrier is a solid and the composition is a tablet. The invention also encompasses a pharmaceutical composition as hereinabove described wherein the carrier is a gel and the composition is a suppository. The invention further 30 encompasses a pharmaceutical composition as hereinabove described wherein the carrier is a liquid and the composition is a solution.

The invention provides a method of treating a subject 35 afflicted with epilepsy which comprises administering to the subject an amount of the compound according to the invention effective to treat epilepsy in the subject.

-10-

The invention also provides a method of treating a subject afflicted with affective illness which comprises administering to the subject an amount of the compound according to the invention effective to treat the
5 affective illness in the subject.

The invention additionally provides a method of treating a subject afflicted with cognitive disorders which comprises administering to the subject an amount of the
10 compound according to the invention effective to treat cognitive disorders in the subject.

The invention further provides a method of treating a subject afflicted with neurodegenerative disease which comprises administering to the subject an amount of the
15 compound according to the invention effective to treat neurodegenerative disease in the subject.

The invention also provides a method of treating a subject afflicted with dyskinesiae which comprises administering to the subject an amount of the compound according to the invention effective to treat dyskinesiae
20 in the subject.

25 The invention still further provides a method of treating a subject afflicted with neurotoxic injury which comprises administering to the subject an amount of the compound according to the invention effective to treat neurotoxic injury in the subject.

30 The invention provides a method of alleviating convulsions in a subject afflicted with epilepsy which comprises administering to the subject an amount of the compound according to the invention effective to
35 alleviate convulsions in the subject.

The invention also provides a method of treating a subject afflicted with stroke which comprises

- 11 -

administering to the subject an amount of the compound according to the invention effective to treat stroke in the subject.

- 5 The invention additionally provides a method of treating a subject afflicted with brain ischemia which comprises administering to the subject an amount of the compound according to the invention effective to treat brain ischemia in the subject.

10

- The invention still further provides a method of treating a subject afflicted with head trauma injury which comprises administering to the subject an amount of the compound according to the invention effective to treat
15 head trauma injury in the subject.

The compounds of general formulas I and II are potent anticonvulsant agents in conventional models of human epilepsy. Several of the compounds have a surprisingly
20 better therapeutic profile than milacemide, VPA, VPA amide analogs or N-valproyl glycine. Furthermore, they may also be useful in the treatment of other CNS dysfunctions.

- 25 Surprisingly, the compounds of the invention are highly effective in the MES (maximal electroshock), electrical kindling model, and scMet (subcutaneous pentylenetetrazol) tests. The median effective doses (ED₅₀) of the agents claimed herein are considerably lower
30 than those required to produce neurological impairment. Therefore, results in animal models distinguish the compounds of the present invention from other anti-epileptic agents and indicate that some of the disclosed compounds are effective against generalized and partial
35 seizures, in addition to other forms of epilepsy, including absence seizures.

Some of the compounds of this invention possess chiral

-12-

centers. It is a further embodiment of this invention that these compounds may comprise substantially pure D or L enantiomers or racemic mixtures. It is to be understood that compounds of the general formula II may 5 be of the E-(trans) or Z-(cis) geometric configuration, or a mixture thereof.

The compounds of general formula I are diamides of valproic acid and may be prepared via conventional 10 amidation processes, e.g., by reacting an activated form of the aforementioned acid either with an amino acid amide of the general formula III, wherein R₁, R₂, R₃ are the same or different and may be a hydrogen, an alkyl group (C₁-C₆), an aralkyl group or aryl group, and n=0 to 3, or 15 with an amino acid derivative of the general formula IV, in which R₁ and n are the same as for III, and R₄ is hydrogen or a C₁-C₃ alkyl group. The resultant valproyl amino acid derivative V is reacted with amines of the general formula VII (wherein R₄ is a lower alkyl group), 20 or first activated (wherein R₄ is hydrogen), and the activated form of the acid, VI, is then reacted with VII.

- 13 -

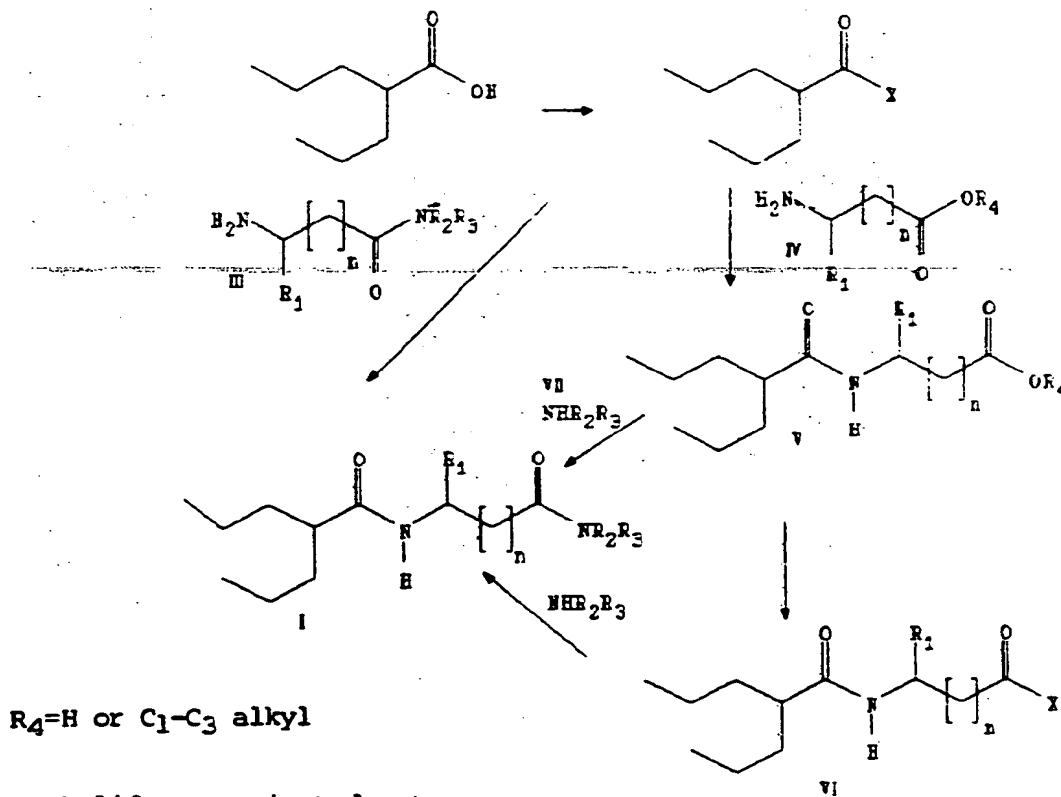
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Thus, compounds I and V may be prepared in a biphasic system consisting of a basic aqueous solution of amino acid amides III or amino acid esters IV and a solution of 30 valproyl chloride in an inert water-immiscible organic solvent, e.g. dichloromethane or toluene, at a temperature ranging between 0 and 50°C, preferably at 0-10°C, for a period of 1 to 24 hrs, preferably 1 to 5 hrs.

35 The basic substance employed for the purpose may be either alkali, such as sodium hydroxide, potassium hydroxide, or potassium carbonate, or an aliphatic or aromatic tertiary amine, preferably triethylamine, and

-14-

must be present in a quantity sufficient to neutralize the hydrohalic acid formed during the reaction.

Compounds I and V may also be prepared by reacting an activated ester of VPA with amino acid amides III or amino acid ester IV. Thus, VPA is reacted with an activating agent, e.g., N-hydroxysuccinimide, pentafluorophenol, pentachlorophenol, or 1-hydroxybenzotriazole, in the presence of a dehydrating reagent such as a dialkylcarbodiimide, e.g., dicyclohexylcarbodiimide, diisopropylcarbodiimide, or N-(dimethylaminopropyl)-N'-ethyl carbodiimide, at a temperature ranging from 0-50°C, preferably at 0-25°C, in an inert solvent, such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, dichloromethane, or N,N-dimethylformamide. The resulting activated ester may be isolated and purified, or used directly in situ. The activated ester, whether purified or used directly, is reacted with III or IV, under the same conditions leading to condensation as detailed hereinabove.

The reaction of compounds V with amines R₂R'NH may be carried out in a wide variety of organic solvents, including in an aprotic solvent which is a saturated or aromatic hydrocarbon, such as hexane, benzene, or petroleum ether, or a halogenated solvent, such as chloroform or dichloromethane, in a protic or alcoholic solvent, such as methanol or ethanol, or water. Preferably, the solvent is methanol. The reaction proceeds effectively at a temperature ranging from ambient to reflux, but preferably at 50-70°C.

Compounds III may be used either as free bases or as their addition salts, formed by treatment of the free bases with an inorganic acid, such as tetrafluoroboric acid, hydrochloric acid, phosphoric acid, or sulfuric acid, or with an organic acid, such as p-toluenesulfonic acid, acetic acid, or benzoic acid. Compounds III may be

-15-

either a pure enantiomeric form, whether of D or L configuration, or a racemic mixture.

The amino acid amides and esters of general formulas III 5 and IV are either commercially available or, alternatively, prepared from appropriate precursors, as detailed in the following examples.

The compounds of general formula II are diamides of 10 valproenoic acid and may be prepared from the latter analogously to the compounds of the general formula I.

Valproenic acid [(E)-2-ene valproic acid] may be prepared according to procedures known in the art. G. Taillandier, 15 et al., Arch. Pharm. (Weinheim), 310, 394 (1977); C.V. Vorhees, et al., Teratology, 43, 583 (1991); R.C. Neuman, Jr., and G.D. Holmes, J. Amer. Chem. Soc., 93, 4242 (1971).

20 In the practice of the invention, the amount of the compound incorporated in the pharmaceutical composition may vary widely. Factors considered when determining the precise amount are well known to those skilled in the art. Examples of such factors include, but are not 25 limited to, the subject being treated, the specific pharmaceutical carrier, and route of administration being employed and the frequency with which the composition is to be administered. A pharmaceutical composition in unit dose form for treatment of the disorders listed 30 hereinabove comprises 10 to 500 mg of the active ingredient.

In a preferred embodiment, the compound is administered 35 in a pharmaceutical composition which comprises the compound and a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutically accepted carriers, such as a phosphate-buffered saline

-16-

solution, water, emulsions such as an oil/water emulsion or a triglyceride emulsion, various types of wetting agents, tablets, coated tablets, and capsules. An example of an acceptable triglyceride emulsion useful in
5 the intravenous and intraperitoneal administration of the compounds is the triglyceride emulsion commercially known as Intralipid®.

Typically, such carriers contain excipients such as
10 starch, milk, sugar, certain types of clay, gelatin, stensic acid, talc, vegetable fats or oils, gums, glycols, or other known excipients. Such carriers may also include flavor and color additives or other ingredients.

15 In the practice of the invention, the administration of the pharmaceutical composition may be effected by any of the well known methods including, but not limited to, oral, intravenous, intraperitoneal, intramuscular or
20 subcutaneous or topical administration. Topical administration can be effected by any method commonly known to those skilled in the art and include, but are not limited to, incorporation of the pharmaceutical composition into creams, ointments, or transdermal
25 patches.

- 17 -

The following Experimental Details are set forth to aid in an understanding of the invention, and are not intended, and should not be construed, to limit in any way the invention set forth in the claims which follow 5 thereafter.

EXAMPLE 1

N-(2-n-Propylpentanoyl)glycinamide. (compound 1)

A solution of valproyl chloride (108 g, 0.66 mole) in 10 CH_2Cl_2 (500 ml) was added dropwise to an ice-cooled solution of glycinamide. HCl (72 g, 0.65 mole), and Et_3N (138 g, 1.37 mole) in water (200 ml). Cooling was discontinued and the two-phase mixture was stirred at RT for 3 hrs, cooled to 5-8°C, and acidified to pH 2 by 15 means of 1N HCl. The solid was collected by filtration, slurried in water (300 ml), filtered, dried and crystallized from EtOAc, affording 75 g (0.375 mole, 50%) of the title compound as a white crystalline solid, mp 127°C.

20

Anal. calc. for $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_2$: C, 59.97; H, 10.06 N, 13.99;
Found: C, 60.09; H, 10.25; N, 14.00.

^1H NMR δ (CDCl_3): 6.72 (br s, 1H, CONH₂), 6.65 (br t, 1H, CONH), 5.75 (br s, 1H, CONH₂), 3.98 (d, 2H, gly $\text{C}\alpha\text{H}_2$), 2.18 (m, 1H, Pr₂CH), 1.57, 1.40 (m, 4H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.29 (m, 4H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 0.89 (t, 6H, CH_3) ppm.
MS: 201 (MH⁺, 100), 184 (MH⁺ - NH₃, 24).
IR: 3240, 3312, 3181, 2953, 2932, 2872, 1676, 1630, 1549,
30 1431, 1325, 1271, 1221 cm^{-1}

EXAMPLE 2

N-(2-n-Propylpentanoyl)leucinamide.

The title compound was prepared from valproyl chloride 35 (2.0 g, 12.3 mmole) and DL-leucinamide hydrochloride (2.0 g, 12.05 mmole), according to the procedure described in Ex. 1. 2.36 g (9.2 mmole, 76%) of a white crystalline solid, mp 151-2°C, was thus obtained.

-18-

Anal. calc. for C₁₄H₂₈N₂O₂: C, 65.58; H, 11.01; N, 10.93;
Found: C, 65.28; H, 10.89; N, 10.86.

5 ¹H NMR δ (DMSO): 7.85 (br d, 1H, CONH), 7.20 (br s, 1H, CONH₂), 6.89 (br s, 1H, CONH₂), 4.27 (m, 1H, leu CαH), 2.25 (m, 1H, Pr₂CH), 1.60, 1.42, 1.20 (m, 11H, CH₃CH₂CH₂, Me₂CHCH₂), 0.88 (d, 3H, leu Me), 0.83 (d, 3H, leu Me), 0.83 (br t, 6H, Me) ppm.

10 MS: 257 (MH⁺, 100), 240 (MH⁺ - NH₃, 32).

IR: 3410, 3300, 2955, 2925, 1720, 1655, 1645, 1540, 1260 cm⁻¹.

15

EXAMPLE 3

N-(2-n-Propylpentanoyl)-2-phenylglycinamide.

A solution of valproyl chloride (1.95g, 12mmole) in 1,2-dimethoxyethane (DME, 30ml) was added to an ice-cooled suspension of phenylglycinamide (1.80g, 20 12mmole, prepared from DL-phenylglycinonitrile, Ger. off. 2637204) and Et₃N (2.4 g, 24 mmole) in DME (35 ml). The reaction mixture was stirred under a nitrogen atmosphere for 24 hrs at RT, and the resultant product was collected by filtration, washed with cold hexane (50ml) and taken into EtOAc/H₂O (200 ml:175 ml). The organic layer was separated, washed successively with satd. NaHCO₃, 0.1N HCl and satd. NaCl, dried and evaporated to dryness. The crude product was crystallized from EtOAc, affording 2.50 g (9.06 mmole, 75%) of the title compound as a white 25 crystalline solid, mp 190-1°C.

Anal. calc. for C₁₆H₂₄N₂O₂: C, 69.53; H, 8.75; N, 10.14;
Found: C, 68.26; H, 8.57; N, 9.96.

35 ¹H NMR δ (DMSO): 8.36 (br d, 1H, CONH), 7.65 (br s, 1H, CONH), 7.46-7.22 (m, 5H, Ph), 7.10 (br s, 1H, CONH₂), 5.46 (d, 1H, Ph-CH), 2.44 (m, 1H, Pr₂CH), 1.40, 1.22, 1.10 (m, 8H, CH₃CH₂CH₂), 0.85 (t, 3H, Me), 0.78 (t, 3H, Me) ppm.

- 19 -

MS: 277 (MH^+ , 56), 201 (100).

IR: 3400, 3300, 2950, 2910, 1735, 1685, 1560, 1400 cm^{-1} .

5

EXAMPLE 4

N-(2-n-Propylpentanoyl)alanine methyl ester.

A solution of DL-alanine methyl ester hydrochloride (13.7 g, 98 mmole) and Et₃N (20.2 g, 200 mmole) in water (50 ml) was added dropwise to an ice-cooled solution of valproyl chloride (15.0 g, 92 mmole) in CH₂Cl₂ (150 ml). After completion of addition the reaction mixture was stirred for 4 hrs. at RT. The layers were then separated and the aqueous layer extracted with CH₂Cl₂. The combined organic phases were washed successively with water, satd. NaHCO₃, 0.1N HCl and satd. NaCl, dried and evaporated to dryness. The residue was treated with hexane (60ml), and the resultant solid was collected by filtration, washed with hexane and dried to give 14.2g (62mmole, 63%) of the title compound as a white solid, mp 72-3°C.

20

¹H NMR δ (CDCl₃): 6.02 (br d, 1H, NH), 4.63 (quintet, 1H, ala CoH), 3.75 (s, 3H, OMe), 2.08 (m, 1H, Pr₂CH), 1.6, 1.4, 1.32 (m, 8H, CH₂CH₂CH₂), 1.40 (d, 3H, ala Me), 0.89 (t, 6H, Me) ppm.

25

MS: 230 (MH^+ , 100), 127 (7), 104 (16).

IR: 3300, 2925, 1740, 1630, 1540 cm^{-1} .

30

EXAMPLE 5

N-(2-n-Propylpentanoyl)glycine methyl ester.

The title compound was prepared from valproyl chloride (19.34g, 119mmole) and glycine methyl ester hydrochloride (15.0g, 119mmole), according to the procedure described in Ex. 4. 22g (102 mmole, 86%) of an off-white solid, mp 68°C, was thus obtained.

¹H NMR δ (CDCl₃): 5.97 (br t, 1H, NH), 4.06 (d, 2H, gly

-20-

CH₂), 3.76 (s, 3H, OMe), 2.14 (m, 1H, Pr₂CH), 1.60, 1.45-1.25 (m, 8H, CH₃CH₂CH₂), 0.90 (t, 6H, Me) ppm.

MS: 216 (M⁺, 100), 127 (13).

5

IR: 3300, 2945, 2920, 1765, 1650, 1550, 1220 cm⁻¹.

EXAMPLE 6

N-(2-n-Propylpentanoyl)alaninamide.

- 10 Aqueous ammonia (25%, 50ml) was added dropwise to a solution of N-(2-propylpentanoyl)alanine methyl ester (6.87g, 30mmole) in methanol (20ml), and the reaction mixture was stirred under reflux for 4 hrs. The solid which precipitated upon cooling was filtered, washed with 15 cold hexane, dried and crystallized from EtOAc to give 1.90g (8.92mmole, 30%) of the title compound as a white crystalline solid, mp 165-166°C.

Anal calc. for C₁₁H₂₂N₂O₂: C, 61.64; H, 10.35; N, 13.08;

20 Found: C, 61.35; H, 10.26; N, 13.32.

¹H NMR δ (DMSO): 7.84 (br d, 1H, CONH), 7.21 (br s, 1H, CONH₂), 6.92 (br s, 1H, CONH₂), 4.25 (quintet, 1H, ala CαH), 2.24 (m, 1H, Pr₂-CH), 1.42, 1.20 (m, 8H, CH₃CH₂CH₂), 1.17 (d, 3H, ala Me), 0.833 (t, 3H, Me), 0.827 (t, 3H, Me) ppm.

MS: 214 (M⁺, 1), 170 (M⁺ - CONH₂, 100).

30 IR: 3390, 3295, 1675, 1620 cm⁻¹.

EXAMPLE 7

N-(2-n-Propylpentanoyl)alanine-N'-benzylamide.

- The title compound was prepared from N-(2-propylpentanoyl)alanine methyl ester (3.67 g, 16 mmole) according to the procedure described in Ex. 6, except that a methanolic solution of benzylamine (1.5 molar excess) was used, and the reaction mixture was stirred under reflux

-21-

for 24 hours. 1.4 g. (4.6 mmole, 29%) of the title compound as a white solid, mp 139°C, was thus obtained.

Anal calc. for C₁₈H₂₈N₂O₂: C, 71.01; H, 9.27; N, 9.21;
 5 Found: C, 70.88; H, 9.15; N, 9.24.

¹H NMR δ (DMSO): 7.25 (m, 6H, PhCH₂NH), 6.40 (br d, 1H, CONH), 4.61 (quintet, 1H, ala CαH), 4.39 (m, 2H, Ph-CH₂),
 2.06 (m, 1H, Pr₂CH) 1.50, 1.25 (m, 8H, CH₃CH₂CH₂), 1.34 (d,
 10 3H, ala Me), 0.87 (t, 3H, Me), 0.82 (t, 3H, Me) ppm.

MS: 304 (M⁺, 34), 198 (M⁺ - PhCH₂NH, 11); 171 (44).

IR: 3280, 2945, 2925, 1640, 1550, 1445 cm⁻¹.

15

EXAMPLE 8

N-(2-Propylpentanoyl)glycine-N'-methylamide.

The title compound was prepared from N-(2-propylpentanoyl)glycine methyl ester (5.0g, 23.2 mmole) and 35% aqueous methylamine (56.4 mmole), according to the procedure described in Ex. 7. 2.86g (13.4 mmole, 58%) of a white crystalline solid, mp 146°C, was thus obtained.

Anal. calc. for C₁₁H₂₂N₂O₂: C, 61.65; H, 10.35; N, 13.07;
 25 Found: C, 61.36; H, 10.14; N, 12.78.

¹H NMR δ (DMSO): 7.99 (br t, 1H, CONHCH₂), 7.69 (m, 1H, CONHCH₃), 3.62 (d, 2H, gly CH₂), 2.58 (d, 3H, NHMe), 2.22
 30 (m, 1H, Pr₂CH), 1.45, 1.22 (m, 8H, CH₃CH₂CH₂), 0.83 (t, 6H, Me) ppm.

MS: 215 (MH⁺, 100), 197 (MH⁺ - H₂O, 23), 184 (MH⁺ - MeNH₂, 65), 127 (8).

35 IR: 3300, 2960, 2920, 2870, 1660, 1630, 1555, 1440, 1420
 cm⁻¹.

- 22 -

EXAMPLE 9

N-(2-n-Propylpentanoyl)glycine-N'-butylamide.

The title compound was prepared from N-(2-propylpentanoyl)glycine methyl ester (5.0 g, 23.0 mmole) and butylamine (4.1 g, 55.0 mmole), according to the procedure described in Ex. 7. 2.2 g (8.5 mmole, 37%), mp 101°C, was thus obtained.

Anal. calc. for C₁₄H₂₈N₂O₂: C, 65.58; H, 11.01; N, 10.93;
10 Found: C, 65.87; H, 11.23; N, 11.38.

¹H NMR δ (DMSO): 7.99 (br t, 1H, NH), 7.65 (br t, 1H, NH),
3.63 (d, 2H, gly CH₂), 3.05 (m, 2H, CH₃CH₂CH₂CH₂NH), 2.22
(m, 1H, Pr₂CH), 1.50-1.16 (m, 12H, CH₃CH₂CH₂),
15 CH₃CH₂CH₂CH₂NH), 0.85 (t, 3H, CH₃CH₂CH₂NH), 0.83 (t, 3H,
CH₃CH₂CH₂) ppm.

MS: 257 (MH⁺, 100), 184 (MH⁺ - C₄H₉NH₂, 19).

20 IR: 3300, 2940, 1660, 1635, 1555, 1470, 1435, 1300 cm⁻¹.

EXAMPLE 10

N-2-n-Propylpentanoyl)glycine-N'-methylamide.

The title compound was prepared from valproyl chloride (404mg, 2.5mmole) and 2-amino-N-methylacetamide (220mg, 2.5mmole, prepared from glycine methyl ester hydrochloride and methylamine), according to the procedure described in Ex. 1. 318 mg (1.49 mmole, 59%) of a white crystalline solid was thus obtained, identical to 30 the product described in Ex. 8.

EXAMPLE 11

N-(2-n-Propylpentanoyl)-4-aminobutyramide.

To an ice-cooled solution of N-(2-propylpentanoyl)-4-aminobutyroyl chloride (prepared from N-(2-propylpentanoyl)-4-aminobutyric acid and SOCl₂, 5.9 g, 24.0 mmole) in dioxane (25ml), was added dropwise conc. NH₄OH (34 ml) over 1 hr. The reaction mixture was then stirred

-23-

at RT for 20 hrs and evaporated to dryness under reduced pressure. The residue was taken up in an H₂O (20 ml) and EtOAc (30ml) mixture, the mixture stirred vigorously for 5 min. The organic phase was separated, evaporated to dryness under reduced pressure, and the residue crystallized from EtOAc to give 1.4 g (6.1 mmole, 26%) of a crystalline solid, mp 138°C.

Anal calc for C₁₂H₂₄N₂O₂: C, 63.13; H, 10.60; N, 12.27;
10 Found: C, 63.12; H, 10.69; N, 12.54.

¹H NMR δ (DMSO): 7.81 (br t, 1H, NH), 7.26 (br s, 1H, (CH₂)₃CONH₂), 6.73 (br s, 1H, (CH₂)₃CONH₂), 3.02 (m, 2H, CH₂CH₂CH₂CONH₂), 2.11 (m, 1H, Pr₂CH), 2.03 (t, 2H, CH₂CONH₂), 15 1.58 (m, 2H, CH₂CH₂CONH₂), 1.42 (m, 2H, CH₂CHCO), 1.19 (m, 6H, CH₂CH₂CHCO), 0.84 (t, 6H, Me) ppm.

MS: 229 (MH₊, 100), 127 (17).

20 IR: 3405, 3300, 3190, 2960, 2935, 2880, 1660, 1655, 1635, 1550, 1445 cm⁻¹.

EXAMPLE 12

N-[2-n-Propylpent-(E)-2-enoyl]glycinamide.

25 A cold solution of glycinamide hydrochloride (6.63g, 60 mmole) in water (18ml) and Et₃N (12.79, 126 mmole) were added slowly to a stirred and ice-cooled solution of (E)-2-ene-valproyl chloride in toluene (40 ml). After completion of addition, the biphasic reaction mixture was 30 stirred at ambient temperature for 3 hrs. Work-up and crystallization according to the procedure in Ex. 1 afforded 6.92 g (34.8 mmole, 58%) of the title compound as a white crystalline solid, mp 112°C.

35 Anal. calcd. for C₁₀H₁₈N₂O₂: C, 60.58; H, 9.13; N, 14.13; Found: C, 60.53; H, 8.86; N, 14.04.

¹H NMR δ (CDCl₃): 6.97 (br s, 1H, CONH₂), 6.91 (br t, 1H,

-24-

NH), 6.29 (t, 1H, vinyl), 6.05 (br s, 1H, CONH₂), 2.28 (m, 2H, CH₃CH₂CH=), 2.17 (m, 2H, CH₃CH₂CH₂), 1.42 (m, 2H, CH₃CH₂CH₂), 1.05 (t, 3H, Me), 0.93 (t, 3H, Me) ppm.

5 MS: 199 (MH⁺, 83), 182 (MH⁺ - NH₃, 79), 125 (100).

IR: 3341, 3179, 2955, 2872, 1680, 1601, 1535, 1433, 1319 cm⁻¹

10

EXAMPLE 13

N-[2-n-Propylpent-(E)-2-enoyl]alanine methyl ester.

The title compound was prepared from (E)-2-enevalproyl chloride (10.95g, 68.1 mmole) and alanine methyl ester hydrochloride (10.14 g, 72.6 mmole) according to the 15 procedure described in Ex. 4. The crude product was crystallized from hexane to give 13.25g (58.4 mmole, 86%) of a white crystalline solid, mp 25°C.

1H NMR δ (CDCl₃): 6.30 (br d, 1H, NH), 6.23 (t, 1H, vinyl)
20 4.65 (m, 1H, ala CH), 3.76 (s, 3H, OMe), 2.29 (m, 2H, CH₃CH₂CH=), 2.17 (m, 2H), 1.43 (d, 3H, ala CH₃), 1.43 (m, 2H, CH₃CH₂CH₂), 1.04 (t, 3H, Me), 0.92 (t, 3H, Me) ppm.

MS: 228 (MH⁺, 100), 196 (NH⁺+ - NH₃, 100), 168 (30), 125
25 (76).

EXAMPLE 14

N-[2-n-Propylpent-(E)-2-enoyl]glycine-N'-methylamide.

The title compound was prepared from N-[2-n-propylpent-(E)-2-enoyl]glycine methyl ester (13.5g, 63.9 mmole), prepared from 2-enevalproyl chloride and glycine methyl ester hydrochloride as described in Ex. 5, and 35% aqueous methylamine (15 ml, 169.2 mmole), according to the procedure described in Ex. 7. The amide product was 35 purified by column chromatography and crystallized from EtOAc to give 7.8g (36.8 mmole, 58%) of a white crystalline solid, mp 68-9°C.

-25-

Anal. calcd. for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20;
Found: C, 62.42; H, 9.50; N, 13.05.

- ¹H NMR δ (DMSO): 7.94 (br t, 1H, NH) 7.67 (m, 1H, NHCH₃) ,
5 6.23 (t, 1H, vinyl), 3.65 (d, 2H, gly), 2.58 (d, 3H,
NHCH₃) , 2.21 (m, 2H, CH₃CH₂CH=), 2.13 (m, 2H, CH₃CH₂CH₂),
1.32 (m, 2H, CH₃CH₂CH₂), 0.99 (t, 3H, Me), 0.85 (t, 3H, Me)
ppm.
- 10 MS: 213 (MH⁺, 73), 195 (37), 182 (MH⁺ - CH⁺3NH₂, 100), 125
(74).

IR: 3300, 2955, 2925, 1660, 1620, 1560, 1540, 1460 cm⁻¹.

15

EXAMPLE 15

N-[2-n-Propylpent-(E)-2-enoyl]alaninamide.

The title compound was prepared from N-[2-n-propylpent-(E)-2-enoyl]alanine methyl ester (9.08g, 40 mmole) and aqueous ammonia (67 ml), in a manner analogous to that
20 described in Ex. 6, giving 5.0g (59%) of a white crystalline solid, mp 141-2°C.

Anal. calcd. for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20;
Found: C, 62.48; H, 9.25; N, 13.18.

25

¹H NMR δ (DMSO): 7.63 (d, 1H, NH) 7.25 (br s, 1H, CONH₂),
6.96 (br s, 1H, CONH₂), 6.18 (t, 1H, vinyl) 4.25 (m, 1H,
ala CH), 2.21 (m, 2H, CH₃CH₂CH₂), 1.31 (m, 2H, CH₃CH₂CH=),
2.11 (m, 2H, CH₃CH₂CH₂), 1.31 (m, 2H, CH₃CH₂CH₂), 1.23 (d,
3H, ala CH₃), 0.99 (s, 3H, Me), 0.84 (s, 3H, Me) ppm.

MS: 213 (MH⁺, 74), 196 (MH⁺ - NH₃, 100), 125 (76).

IR: 3725, 3180, 2950, 1700, 1650, 1605, 1530, cm⁻¹

35

EXAMPLE 16

N-(2-n-Propylpentanoyl)- β -alaninamide.

A mixture of N-(2-n-propylpentanoyl)- β -alanine ethyl ester

-26-

(4.45g, 18.29 mmole), prepared from valproyl chloride and β -alanine ethyl ester hydrochloride according to the procedure described in Ex. 4, dry formamide (2.74g, 61.27 mmole) and anhydrous THF (9.2 ml) was heated to 100°C, 5 and a freshly prepared solution of sodium methoxide (12.7 mmole) in MeOH (2.93 ml) was added dropwise over 20 min. The mixture was heated at 100°C for 4 hours and isopropanol (100 ml) was added. The suspension was heated to reflux, filtered, and the filtrate was 10 evaporated to dryness. The residue was dissolved in a refluxing mixture of water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (4x100 ml). The combined organic layers were washed with water, dried, and evaporated to dryness. The crude 15 product (2.5 g) was crystallized from EtOAc to give 2.20 g (10.28 mmole, 56%) of a white solid, mp 167-8°C.

Anal. calcd. for $C_{11}H_{22}N_2O_2$: C, 61.64; H, 10.35; N, 13.08.
Found: C, 61.41; H, 10.16; N, 12.91.

20

1H NMR δ (DMSO): 7.82 (br t, 1H, CONH), 7.29 (br s, 1H, CONH₂), 6.79 (br s, 1H, CONH₂), 3.20 (q, 2H, β -ala), 2.21 (t, 2H, α -ala), 2.12 (m, 1H, (Pr)₂CH), 1.41, 1.18 (m, 8H, CH₂CH₂CH₂), 0.83 (t, 6H, Me) ppm.

25

MS: 215 (MH⁺, 100), 197 (MH⁺ - NH₃, 69), 172 (13), 127 (3).

30

IR: 3389, 3303, 3202, 2957, 2928, 1653, 1634, 1551, 1456, 1439 cm⁻¹.

EXAMPLE 17

N-(2-n-Propylpentanoyl)threoninamide.

A solution of valproyl chloride (3.15g, 19.4 mmole) in 35 anhydrous 1,2-dimethoxyethane (DME, 48 ml) was added slowly to a suspension of threoninamide hydrochloride (3.0g, 19.4 mmole) and Et₃N (3.88 g, 38.8 mmole) in anhydrous DME (60 ml) at 10-15°C. The reaction mixture

- 27 -

was stirred for 24 hours at RT under N₂; the solvent was removed under reduced pressure, and the residue was worked up in a manner analogous to that in Ex. 16. The product was crystallized from EtOAc to give 1.0g (4.1 mmole, 21%) of a white solid, mp 172-4°C.

Anal. calcd. for C₁₂H₂₄N₂O₃: C, 58.99, H, 9.90; N, 11.47;
Found: C, 58.12; H, 9.42; N, 11.43.

10 ¹H HMR δ (DMSO): 7.58 (d, 1H, CONH), 7.05 (br s, 2H, CONH₂), 4.84 (d, 1H, OH), 4.18 (dd, 1H, α-thr, 3.99 (m, 1H, β-thr); 2.35 (m, 1H, -Pr₂CH), 1.44, 1.22 (m, 6H, CH₃CH₂CH₂), 1.02 (d, 3H, Me-thr), 0.85 (t, 3H, Me), 834 (t, 3H, Me) ppm.

15

MS: 245 (MH⁺, 37), 228 (MH⁺ - NH₃, 100).

IR: 3405, 3281, 2957, 2930, 2854, 1688, 1665, 1624, 1549 cm⁻¹.

20

EXAMPLE 18

N-(2-n-Propylpentanoyl)glycine-N',N'-dimethylamide.

N-(2-n-Propylpentanoyl)glycine methyl ester (6.0 g, 29.9 mmole) prepared from valproyl chloride and glycine methyl ester hydrochloride according to the procedure in Ex. 4 was dissolved in MeOH (15 ml) and 40% aqueous dimethylamine (11 ml) was added dropwise. The reaction mixture was refluxed for 19 hr and evaporated to dryness. The reaction mixture was treated with hot ethyl acetate, cooled, and filtered. The filtrate was washed consecutively with sat. NaHCO₃ and sat. NaCl solution, dried and evaporated to dryness. The solid residue was crystallized from ethyl acetate/hexane to give 1.50g of a white solid, mp 78-80°C.

35

Anal. calcd. for C₁₂H₂₄N₂O₂: C, 63.12, H, 10.59; N, 12.27.
Found: C, 62.80, H, 10.64; N, 11.93.

-28-

¹H NMR δ (DMSO): 7.73 (br t, 1H, CONH), 3.79 (d, 2H, gly),
2.84 (s, 3H, Me), 2.72 (s, 3H, Me), 2.16 (m, 1H, (Pr)₂CH),
1.34 (m, 2H), 1.12 (m, 6H), 0.74 (t, 6H, Me) ppm.

5 MS: 229 (MH⁺, 100), 184 (18).

IR: 3314, 2951, 2924, 2872, 1662, 1630, 1522, 1466 cm⁻¹.

10

EXAMPLE 19

Biological Activity of N-(2-Propylpentanoyl)glycinamide.
All compounds provided herein were screened for their ability to protect against chemically and electrically induced convulsions, in at least two different models of 15 epilepsy. The first model, the subcutaneous pentylenetetrazol (s.c. Met) seizure threshold test, is a standard screening procedure to show efficacy for agents against absence seizures. The second model, the maximal electroshock (MES) test, is used to show efficacy 20 for antiepileptic agents against generalized seizures. In these studies, convulsions were inhibited or prevented in mice after intraperitoneal (i.p.) administration and/or in rats after oral (p.o.) administration of the compounds.

25

N-(2-Propylpentanoyl)glycinamide (hereinafter compound 1) was further tested in two additional models. The third model, electrical kindling of rats, has been known to show efficacy of antiepileptic agents against complex 30 partial seizures that evolve into generalized motor seizures. In these tests, rats were electrically stimulated via corneal electrodes twice daily for approximately 5 days and then once daily for an additional 10 days. Once the seizure criteria, as 35 described by R.J. Racine, et al., Electroenceph. Clin. Neurophysiol., 32: 281-294 (1972), were met, the test substance was administered p.o. to rats, and the rat electrically stimulated, and observed for the presence or

-29-

absence of a seizure. In addition, compound 1 was also tested in the subcutaneous bicuculline model (s.c. Bic). For detailed procedures of all the above test models, see E.A. Swinyard, et al., in "Antiepileptic Drugs," ed. by 5 R.H. Levy, et al., Raven Press, New York, at 85-100 (1989) and Racine, Id.

Compound 1 showed anticonvulsant activity in rodents in all of the above mentioned tests (MES, s.c. Met, s.c. 10 Bic, and electrical kindling models). The ED₅₀ (rat, p.o.) in the MES model was 73 mg/kg (Table 1). This value is seven times lower (more efficacious) than that found for VPA, and approximately twice that found for phenytoin (Table 1; see E.A. Swinyard, et al., id.). 15 Further, in the electrically kindled rat model, compound 1 (administered p.o.) prevented seizures with an ED₅₀ of 162 mg/kg (Table 1). The results are therefore indicative of compound 1 having an efficacy against generalized seizures and complex partial seizures which 20 evolve into generalized motor seizures.

In addition, in the s.c. Bic model, compound 1 provided full protection from seizures in mice, at a dose that was approximately that of literature values for the ED₅₀ for 25 VPA. Literature values also show that phenytoin, considered the drug of choice for partial and generalized tonic-clonic seizures, is not effective in this model. See B.J. Wilder and R.J. Rangel, in "Antiepileptic Drugs," ed. by R.H. Levy, et al., Raven Press, New York, 30 at 233-239 (1989).

In the s.c. Met model (mice, i.p.), the ED₅₀ for compound 1 was 127 mg/kg (Table 1) as compared to the literature value of 146 mg/kg for VPA. These results further 35 indicate efficacy for compound 1 against absence seizures as well.

-30-

EXAMPLE 20

Neurotoxicity of Compound 1.

Neurotoxicity of the claimed agents was also assessed in mice (i.p. administration) by the rotorod ataxia test and 5 also in some cases in rats (p.c. administration) by the positional sense test and gait and stance test. See E.A. Swinyard, et al., in "Antiepileptic Drugs," ed. by R.H. Levy, et al., Raven Press, New York, at 85-100 (1989). None of the agents provided in the invention showed 10 neurotoxicity in mice at the test dose of 100 mg/kg. Compound 1 had a median neurological toxic dose (TD_{50}) in rats of more than 1000 mg/kg. By comparison, the TD_{50} for VPA was 280 mg/kg. In mice, the difference between TD_{50} values between compound 1 and VPA was smaller, but still 15 significantly higher for compound 1 (less neurotoxic) (Table 1). The protective index (PI, $PI=TD_{50}/ED_{50}$) for compound 1 in rats tested in the MES test is more than 23 times greater than that found for VPA (Table 1). These results are shown to indicate that there is a larger 20 therapeutic dose range that can be administered before neurological side effects are usually observed.

The median lethal dose (LD_{50}) of compound 1 in mice (i.p. administration) is more than 4,000 mg/kg. This value is 25 in contrast to VPA whose LD_{50} in the same test was 658 mg/kg. The results, therefore, indicate that compound 1 is considerably less toxic than VPA.

EXAMPLE 21

30 Neurological Activity of Compound 1.

A major neurological side effect observed in patients on treatment with antiepileptic agents is cognitive impairment. Present data further indicate that at the minimum dose required to provide full protection from 35 seizures induced in rats in the MES test, compound 1 results in less cognitive impairment than VPA. Results from the models used are taken as indicators of major constituents of human cognition.

-31-

- The studies test for the level of motivation, association and short and long-term memory. The specific studies were the effect of compound 1 on the performance of rats in the locomotor test and passive and active response tests. In the cognitive studies below, doses used for compound 1 and VPA were the minimum doses which give full protection against seizures in the MES test (Compound 1 = 200 mg/kg and VPA = 500 mg/kg).
- 10 In the locomotor test, motor activity was recorded 8 to 9 days after the beginning of drug treatment. Locomotion scores were recorded in cages (25x26cm) having a grid of infra-red beams at 4cm intervals. Two categories of movements were recorded: small movements (those originating in stationary activities such as grooming and scratching), and big movements (those resulting in ambulation and recorded as the simultaneous crossing of more than two beams). Since rats are nocturnal animals, recordings were usually made between 18:00 PM - 6:00 AM.
- 20 The results in the locomotor test (Table 2) show no significant difference in motor activity between the control and compound 1.
- 25 To measure passive avoidance responses, tests were performed on days 10, 12, 14, 20, and 26 after initiation of drug treatment. The apparatus consisted of a lit chamber that can be separated from a dark chamber by a sliding door. In the experiment, a rat is placed in a
- 30 lit chamber for 30 sec, the door is then opened and the rat moves into the dark chamber with latency that is recorded. Upon entry into the dark chamber, the door is shut and a 0.3 mA footshock is delivered for 3 sec. Retention of the experience is determined after 48 hours
- 35 by repeating the test and recording the latency. The maximum latency was arbitrarily assigned the value of 300 sec. Longer latencies are taken as a measure of improved memory.

- 32 -

- Results from this study show that on day 16 of the test, the group receiving compound 1 retained their acquired knowledge to avoid the electric shock as well as the control group (Figure 1). The VPA-treated rats, however, 5 were apparently affected by treatment, and performed much worse. These results suggest that VPA adversely affected memory, whereas compound 1 did not have this adverse effect.
- 10 The conditioned avoidance response (active avoidance test) of rats was determined in a Hugo-Basile automatic conditioning apparatus, which consists of a shuttle box with two separate floor grids. In this apparatus the rats are conditioned to jump from one side of the box to 15 the other side. The conditioning is a 10 sec stimulus consisting of a light and electric buzzer. At the end of this stimulus the rats which do not jump to the other side of the box receive a 20 sec electroshock (50V, 0.3mA) from the grid floor. The rats that do jump to the 20 other side of the box do not receive the shock. The session is then repeated with the same rats 7 days later. Experiments were carried out on days 16-17 and 22-23 from the start of drug treatment, and each rat received 60 trials with a 30 sec interval between each trial.
- 25
- The following parameters were recorded: a) the number of potential shocks successfully avoided; b) the latency response in seconds for avoiding a potential shock; and c) the total number of crossings made throughout the 30 trials. In this test, a better performance is indicated by an increase in the avoidance of an electric shock, a decrease in the latency time to jump to the other side of the cage, and an increase in the number of times the rats crossed to the other side of the cage.
- 35
- Rats treated with compound 1 showed a significantly better performance than the VPA treated group. The performance of the animals treated with compound 1 was

- 33 -

similar to that of the control group, whereas the VPA-treated rats had a worse performance (Figure 2 and Table 3).

- 5 The tests stated hereinabove are consistent with the conclusion that compound 1 causes less cognitive impairment than VFA.

Based on the lower ED₅₀ and on the higher TD₅₀ and LD₅₀ values of compound 1, as compared to those of VPA, the former may be considered to act by a unique mechanism, and not as a prodrug of VPA. Moreover, these results are quite unexpected in view of the fact that neither valproylglycine nor milacemide was active when tested in mice (i.p. administration at doses up to 300 mg/kg), in the MES and s.c. Met models.

EXAMPLE 22

N-(2-n-Propylpentanoyl)aminoacetonitrile

- 20 A solution of valporyl chloride (3.26g, 20mmole) in toluene (20ml) was added dropwise to a stirred and ice-cooled solution of aminoacetonitrile.HCl (1.85g, 20mmole) and Et₃N (4.24g, 42mmole). The reaction mixture was stirred at ambient temperature for 3 hours; toluene (10ml) and water (10ml) were then added and the phases separated. The toluene layer was diluted in CH₂Cl₂ (80ml) and the phases separated. The organic layer was dried (magnesium sulphate) and evaporated to dryness under reduced pressure. The residue was treated with hexane (30ml, 2hr stirring at RT) and the resulting suspension was filtered and washed with hexane (10ml). The crude product was crystallized from 6:1 hexane:EtOAc to give 2.41g (13.22mmole, 66%) of a white crystalline solid; mp 76-77°C.

35

Anal. Calc.for C₁₀H₁₈N₂O: C, 65.90; H, 9.95; N, 15.37.

Found: C, 65.90; H, 10.22; N, 15.51.

- 34 -

¹H-NMR δ (CDCl₃): 6.40(br s, 1H, NH), 4.19 (d, 2H, CH₂), 2.19
(m, 1H, Pr₂CH), 1.60, 1.42 (m, 4H, CH₂CH₂CH₂), 1.29 (m, 4H, CH₃CH₂CH₂)

0.90 (t, 6H, CH₃) ppm.

5

MS: 183 (MH⁺, 100), 156 (MH⁺-HCN, 19), 127 (23)

IR: 3287, 2959, 2930, 2250, 1657, 1543, 1466, 1420,
1260 cm⁻¹

10

EXAMPLE 23

N-(2-n-Propylpentanoyl)-N-methyl-glycine ethyl ester

A solution of sarcosine ethyl ester-HCl (3.26g, 21.2mmole) and Et₃N (4.37g, 43.3mmole) in 12ml water was added dropwise to an ice-cooled solution of valroyl chloride (3.25g, 20mmole) in CH₂Cl₂ (35ml). The mixture was stirred under reflux for 3 hours and then cooled to room temperature. The phases were separated and the organic layer was washed successively with water (15ml), saturated sodium hydrogen carbonate (15ml) and 0.1N HCl (15ml). The residue was then dried (magnesium sulphate) and evaporated to dryness under reduced pressure affording the title compound as a yellowish oil (15.2mmole, 76%).

25

¹H-NMR δ (CDCl₃): 4.18 (q, 2H, Et), 4.13 (s, 2H, CH₂), 3.12 (s, 3H, CH₃), 2.74 (m, 1H, Pr₂CH), 1.65, 1.35 (m, 8H, CH₃CH₂CH₂), 1.27 (t, 3H, Et), 0.90 (t, 6H, CH₃) ppm.

MS: 244 (MH⁺, 100), 201 (28), 198 (25, MH⁺-EtOH)

30

EXAMPLE 24

N-(2-n-Propylpentanoyl)-N-methyl-glycinamide

To a solution of N-(2-n-propylpentanoyl)-N-methyl-glycine ethyl ester (1.0g, 4.1mmole) in 3ml ethanol, 6.8ml of aqueous ammonium hydroxide was added. The reaction mixture was stirred under reflux for 15 hours and evaporated to dryness under reduced pressure. The residue was taken up in EtOAc (5ml) and the solution washed with

- 35 -

aqueous sodium hydrogen carbonate (5ml), 0.1N HCl (2x5ml) and finally with saturated NaCl (5ml), dried (magnesium sulphate) and evaporated to dryness under reduced pressure. The crude product was treated with hexane 5 (2x2ml), filtered and dried to give 120mg (14%) of the title compound as a white solid; mp 138-140°C.

¹H-NMR δ (CDCl₃): 6.32 (br s, 1H, CONH₂), 5.45 (br s, 1H, CONH₂), 4.02 (d, 2H, glyCH₂), 3.17 (s, 3H, NCH₃), 2.70 (m, 1H, Pr₂CH), 10 1.60, 1.40 (m, 4H, CH₃CH₂CH₂), 1.25 (m, 4H, CH₃CH₂CH₂), 0.90 (t, 6H, CH₃).

MS: 215 (MH⁺, 100), 198 (MH⁺-NH₃, 46), 172 (5), 158 (9).

15

EXAMPLE 25

Various compounds were tested for biological activity and neurotoxicity in the maximal electroshock (MES) test and subcutaneous pentylenetetrazol (s.c. Met) seizure threshold models, in mice (ip), rats (p.o.) or both as 20 indicated, according to the procedures of Examples 19 and 20. Experimental results are presented in Table 4.

Table 1: Anticonvulsant profile of the claimed and reference antiepileptic agents.

	COMPOUND	COMPOUND 1 (mg/kg)	Phenytoin (mg/kg)	Valproic acid (mg/kg)	Carbamazepine (mg/kg)
5	Rat P.o. TD50 MES model	>1000	>3000	281	81.3
	ED50 PI	73 >13.7	29.8 100	490 0.6	8.5 95.7
	s.c. MET model	-	N.E.	-	N.E.
	ED50 PI	-	-	180 1.6	-
10	Electrical kindling model	162	-	117	28.9
	ED50	-	-	-	-
15	Mice i.p. TD50 MES model	369	65.5	426	71.6
	ED50 PI	152 2.4	9.5 6.9	272 1.6	8.8 8.1
	s.c. MET model	-	N.E.	-	N.E.
	ED50 PI	127 2.9	-	149 2.9	-
20	-	-	-	-	-
	-	-	-	-	-

The anticonvulsant profile of compound 1 compared to literature values (for anticonvulsant activity whose experimental protocols were identical to those carried out in the current study) for the prototype anticonvulsant agents VPA and phenytoin. Convulsions were induced in mice and rats by subcutaneous administration of pentylentetrazol (s.c. Met test) or by electrical stimulation (MES test). N.E. = not effective.

Table 2: Activity scores of rats chronically treated with compound 1.

Treatment	Day activity 14.00-20.00h		Night activity 20.00-08.00h		Total mov.
	Big mov.	Total mov.	Big mov.	Total mov.	
Control (7)	1939±349	6391±983	6124±489	23750±2075	
Compound 1 (7)	2402±307	7749±1188	7217±765	22568±2209	
Na Valproate 500mg/kg (6)	2784±352	8963±1554	5832±854	18876±2039	
					1.0

5

10

Activity scores of drug-treated rats, measured in activity cages on days 8-9 after initiation of daily oral dosing with the given drug. Figures are number of crossings±SEM. Number of rats per group are given in parenthesis.

15

Table 3. Active avoidance response of claimed and reference compounds.

Drug treatment	Session I			Session II	
	Avoidance	Latency	Crossings	Avoidance	Latency
Control (7)	9±5	23±3	32±10	9±5	25±2
Compound 1 200mg/kg (7)	14±7	21±3	38±13	12±7	22±3
Carbamazepine 15mg/kg (4)	7±4	27±2	18±10	2±2	29±1
Na Valproate 500 mg/kg (6)	2±3	28±0.4	13±2	6±5	27±2

Scores in the active avoidance test (conditioned avoidance response) of rats treated with compound 1 and related drugs. The tests in the first session were performed on days 16-17 from initiation of drug administration. Those in session II were performed on days 22-23, that is 7 days following session I. Number of rats in a group are given in parenthesis.

Table 4. Biological activity and neurotoxicity of various claimed compounds.

5 COMPOUND	MICE (ip)			MICE (ip)		
	MES ED50	PI	TD50	scMet ED50	PI	TD50
10 1	152	2.4	370	127	2.9	370
	<300	>1	>300	108	2.9	315
3	207	1.5	315	154	<1	170
8	170	1	170	>100	1	>100
2	<100	>1	>100	150	1.5	230
9	80	2.9	230	131	1	157
12	107	1.5	157	<300	<300	<300
14	<300	>1	>100	>1	>100	>100
18	<100	>1				
22						

Table 4 (cont'd)

20 COMPOUND	RAT (po)			RAT (po)		
	MES ED50	PI	TD50	scMet ED50	PI	TD50
1	73	13.7	1000	250	4	1000
8	75	2	150	250	2	500
12	60	8.3	500			

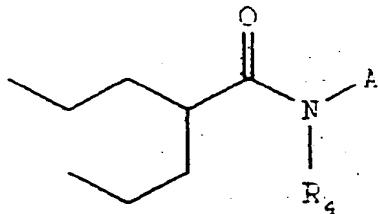
Values are given in mg/kg. The compounds are identified by their example number (e.g., compound 22 is N-(2-n-propylpentanoyl)aminoacetonitrile, disclosed in synthesis Example 22.)

- 40 -

What is claimed is:

1. A compound having the structure:

5

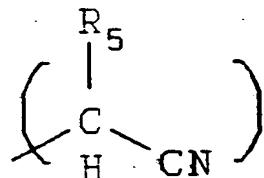


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wherein A is X or Y,

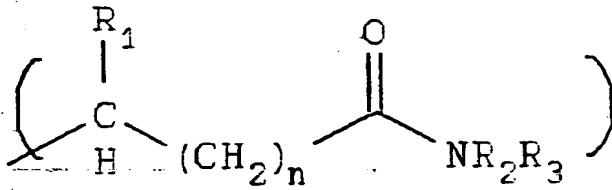
X comprises

15



Y comprises

20



25

R₁, R₂, R₃, R₄ and R₅ are each independently hydrogen,

a C₁-C₆ alkyl group,

an aralkyl group, or

30 an aryl group;

and n is 0, 1, 2, or 3.

;

2. The compound of claim 1, wherein

A is Y; and

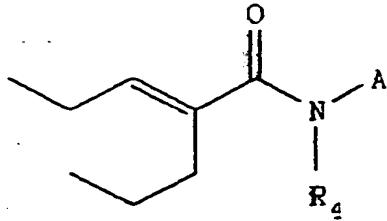
35 R₄ is hydrogen.

3. The compound of claim 1, wherein the C₁-C₆ alkyl group is a linear chain alkyl group.

- 41 -

4. The compound of claim 1, wherein the C₁-C₆ alkyl group is a branched chain alkyl group.
5. The compound of claim 1, wherein the aralkyl group is a benzyl, alkylbenzyl, hydroxybenzyl, alkoxy carbonylbenzyl, aryloxycarbonylbenzyl, carboxybenzyl, nitrobenzyl, cyanobenzyl, or halobenzyl group.
- 10 6. The compound of claim 1, wherein the aryl group is a phenyl, naphthyl, anthracenyl, pyridinyl, indolyl, furanyl, alkylphenyl, hydroxyphenyl, alkoxy carbonylphenyl, aryloxycarbonylphenyl, nitrophenyl, cyanophenyl, halophenyl group, mercaptophenyl, or aminophenyl group.
- 15 7. A compound of claim 1 selected from the group consisting of:
- N-(2-n-propylpentanoyl)glycinamide;
- 20 N-(2-n-propylpentanoyl)-N-methyl-glycinamide;
- N-(2-n-propylpentanoyl)glycine-N'-methylamide;
- N-(2-n-propylpentanoyl)glycine-N'-butylamide;
- N-(2-n-propylpentanoyl)leucinamide;
- N-(2-n-propylpentanoyl)alanine-N'-benzylamide;
- 25 N-(2-n-propylpentanoyl)alaninamide;
- N-(2-n-propylpentanoyl)-2-phenylglycinamide;
- N-(2-n-propylpentanoyl)-4-aminobutyramide;
- N-(2-n-propylpentanoyl)-β-alaninamide;
- N-(2-n-propylpentanoyl)threoninamide;
- 30 N-(2-n-propylpentanoyl)glycine-N',N'-dimethylamide;
- and N-(2-n-propylpentanoyl)aminoacetonitrile.
8. A compound having the structure:

35

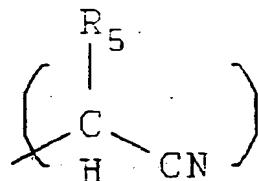


- 42 -

wherein A is X or Y,

X comprises

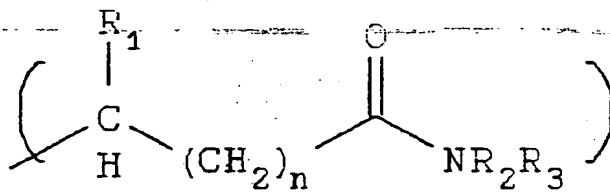
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10

Y comprises

15



R₁, R₂, R₃, R₄ and R₅ are each independently
hydrogen,

a C₁-C₆ alkyl group,
an aralkyl group, or
an aryl group;
and n is 0, 1, 2, or 3.

9. The compound of claim 8 wherein:

25 A is Y; and
R₄ is hydrogen.

10. The compound of claim 8, wherein the C₁-C₆ alkyl group is a linear chain alkyl group.

30 11. The compound of claim 8, wherein the C₁-C₆ alkyl group is a branched chain alkyl group.

35 12. The compound of claim 8, wherein the aralkyl group is a benzyl, alkylbenzyl, hydroxybenzyl, alkoxy carbonylbenzyl, aryloxy carbonylbenzyl, carboxybenzyl, nitrobenzyl, cyanobenzyl, or halobenzyl group.

-43-

13. The compound of claim 8, wherein the aryl group is a phenyl, naphthyl, anthracenyl, pyridinyl, indolyl, furanyl, alkylphenyl, hydroxyphenyl, alkoxy carbonylphenyl, aryloxycarbonylphenyl, nitrophenyl, cyanophenyl, halophenyl group, mercaptophenyl, or aminophenyl group.
14. A compound of claim 8 selected from the group consisting of:
 - 10 N-(2-n-propylpent-2-enoyl)glycinamide;
 - N-(2-n-propylpent-2-enoyl)alaninamide; and
 - N-(2-n-propylpent-2-enoyl)glycine-N'-methylamide.
15. A pharmaceutical composition which comprises the compound of claims 1 or 8 or a pharmaceutically acceptable salt thereof in a therapeutically effective amount and a pharmaceutically acceptable carrier.
- 20 16. The pharmaceutical composition of claim 15 wherein the therapeutically effective amount is an amount from about 10 to about 500 mg.
- 25 17. The pharmaceutical composition of claim 16, wherein the carrier is a solid and the composition is a tablet.
- 30 18. The pharmaceutical composition of claim 16, wherein the carrier is a gel and the composition is a suppository.
- 35 19. The pharmaceutical composition of claim 16, wherein the carrier is a liquid and the composition is a solution.
20. A method of treating a subject afflicted with epilepsy which comprises administering to the subject an amount of the compound of claims 1 or 8

- 44 -

effective to treat epilepsy in the subject.

21. A method of treating a subject afflicted with affective illness which comprises administering to the subject an amount of the compound of claims 1 or 8 effective to treat the affective illness in the subject.
5
22. A method of treating a subject afflicted with cognitive disorders which comprises administering to the subject an amount of the compound of claims 1 or 8 effective to treat cognitive disorders in the subject.
10
23. A method of treating a subject afflicted with neurodegenerative disease which comprises administering to the subject an amount of the compound of claims 1 or 8 effective to treat neurodegenerative disease in the subject.
15
24. A method of treating a subject afflicted with dyskinesiae which comprises administering to the subject an amount of the compound of claims 1 or 8 effective to treat dyskinesiae in the subject.
20
25. A method of treating a subject afflicted with neurotoxic injury which comprises administering to the subject an amount of the compound of claims 1 or 8 effective to treat neurotoxic injury in the subject.
25
26. A method of alleviating convulsions in a subject afflicted with epilepsy which comprises administering to the subject an amount of the compound of claims 1 or 8 effective to alleviate convulsions in the subject.
30
27. A method of treating a subject afflicted with stroke
35

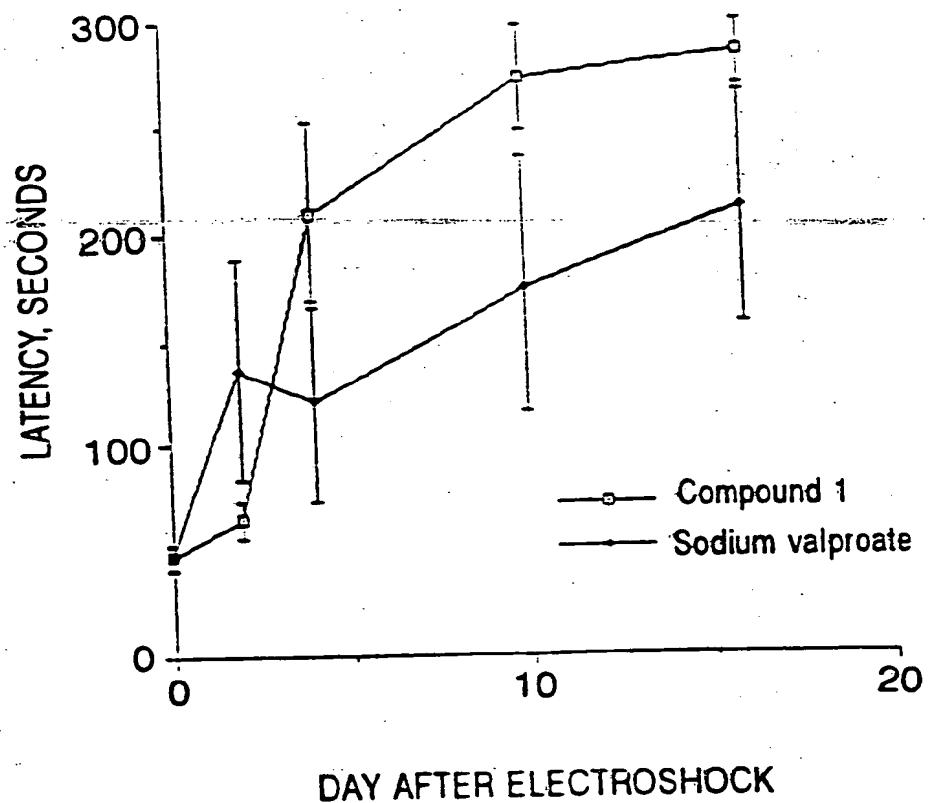
- 45 -

which comprises administering to the subject an amount of the compound of claims 1 or 8 effective to treat stroke in the subject.

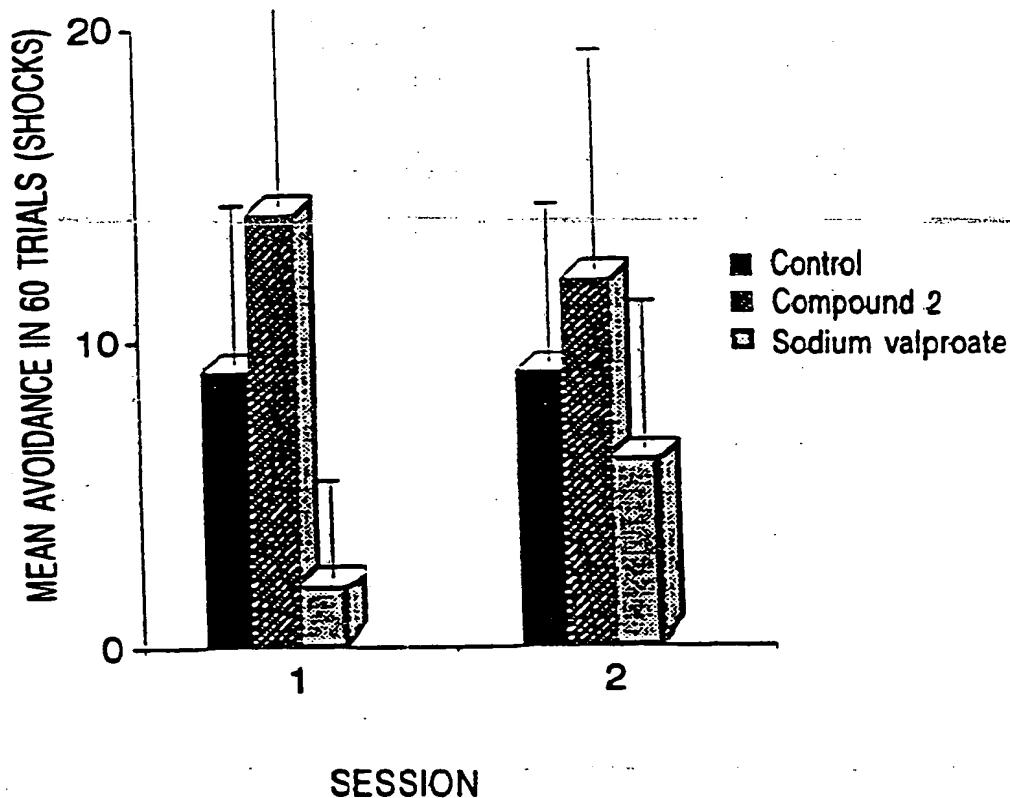
- 5 28. A method of treating a subject afflicted with brain ischemia which comprises administering to the subject an amount of the compound of claims 1 or 8 effective to treat brain ischemia in the subject.
- 10 29. A method of treating a subject afflicted with head trauma injury which comprises administering to the subject an amount of the compound of claims 1 or 8 effective to treat head trauma injury in the subject.

1/2

FIGURE 1



2/2

FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No. PCT/US94/07498

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 237/12, 237/22; 233/01; A61K 31/16, 31/275
US CL :558/445; 564/155, 159; 514/528, 616

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 558/445; 564/155, 159; 514/528, 616

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A, 0,046,707 (Chambor et al.) 03 March 1982, see entire document.	1-7, 15-20, 26
X	Chemical Abstracts, Vol. 101, No. 17, issued 22 October 1984, Granneman, G.R., "Aspects of the Metabolism of Valproic Acid", see abstract no. 143458y, Xenobiotica 14, (s) pp. 375-87, 194.	8-14

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance		
E earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

02 NOVEMBER 1994

Date of mailing of the international search report

08 NOV 1994

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Faximile No. (703) 305-3230

Authorized officer

Robert Gersl

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/07498

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-20, 26

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07498

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

- I. Claims 1-20, 26 directed to compounds, composition and method of treating epilepsy.
- II. Claim 21, directed to compounds, composition and method of treating affective illness.
- III. Claim 22, directed to compounds, composition and method of treating cognitive disorders.
- IV. Claim 23, directed to compounds, composition and method of treating neurodegenerative diseases.
- V. Claim 24, directed to compounds, compositions and method of treating dyskinesia.
- VI. Claim 25, directed to compounds, compositions and method of treating neurotoxic injury.
- VII. Claim 27, directed to a method of treating stroke.
- VIII. Claim 28, directed to a method of treating brain ischemia.
- IX. Claim 29, directed to a method of treating head trauma injury.

The inventions listed as Groups I-IX do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The additional methods of use of Groups II-IX are properly grouped separately from the composition and first method of group I pursuant to 37 CFR 1.475(d).